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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02025989.1

PRIORITY DOCUMENT

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Anmeldung Nr:
Application no.: 02025989.1
Demande no:

Anmeldetag:
Date of filing: 21.11.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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Process for the preparation of tocopheryl acetate

In Anspruch genommene Prioriät(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D311/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

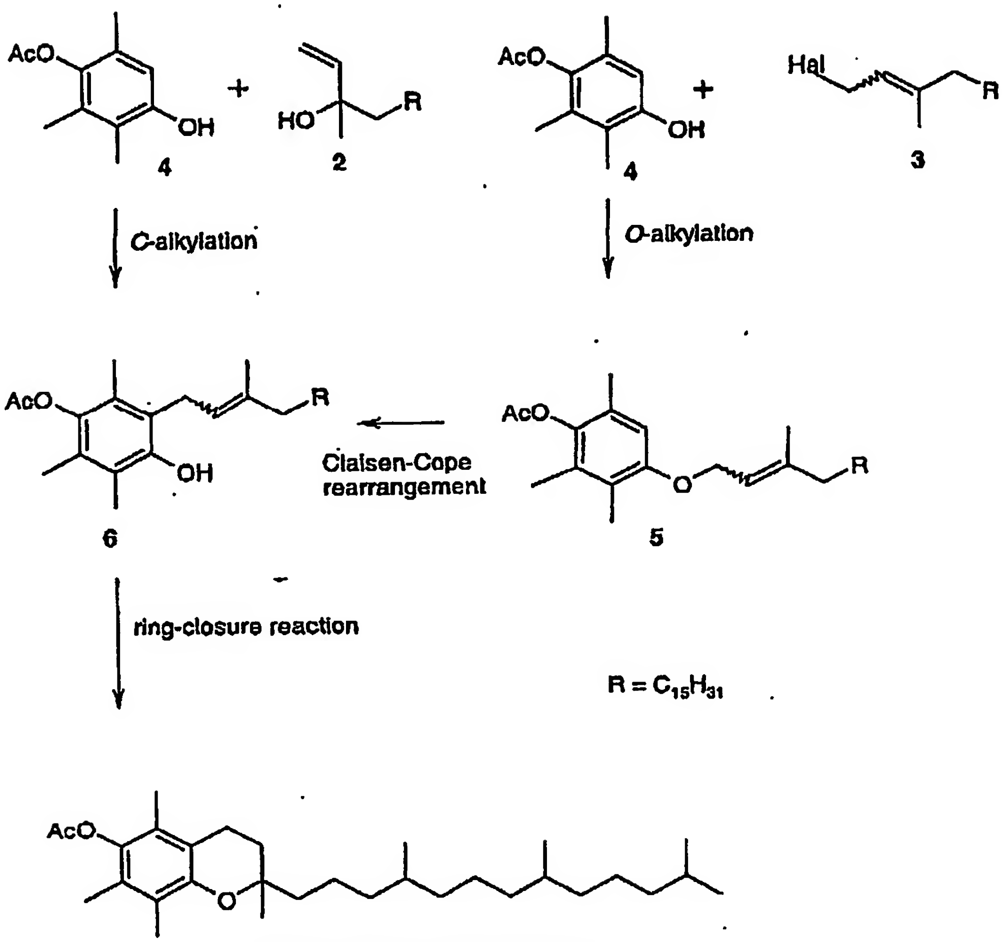
Roche Vitamins AG, CH-4070 Basle, Switzerland

Case 21502

Process for the preparation of tocopheryl acetate

The present invention relates to a novel process for the preparation of tocopheryl acetate and novel intermediates used therein.

Industrial syntheses of vitamin E , α-tocopherol, are based on the reaction of 2,3,5-trimethylhydroquinone with isophytol or phytyl halides, see Ullmann's Encyclopedia of Industrial Chemistry Vol. A27, VCH (1996), pp. 478-488. Since α-tocopherol is labile against oxidative conditions, it is usually converted into its acetate which is more stable and more convenient to handle. Thus, the manufacture of the usual commercial form of vitamin E, viz., tocopheryl acetate, involves the additional step of esterifying α-tocopherol (as obtained by the reaction of of 2,3,5-trimethylhydroquinone with isophytol or phytyl halides). 2,3,5-trimethylhydroquinone, in turn, is obtained from ketoisophorone via 2,3,5-trimethylhydroquinone diacetate and saponification of the latter. The present invention provides a new approach to tocopheryl acetate. According to that approach, 2,3,6-trimethylhydroquinone-1-acetate is reacted with either isophytol or phytol to produce 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate, or with a phytyl halide to produce 4-O-phytyl-2,3,6-trimethylhydroquinone-1-acetate and submitting the latter to conditions resulting in a Claisen-Cope rearrangement to produce 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate and, finally, submitting the 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate to ring closure to obtain tocopheryl acetate. The new approach to α-tocopheryl acetate is shown in the formula scheme depicted below wherein R denotes the remainder of the phytol molecule and Br is representative of a halogen.



(all-*rac*)-α-tocopheryl acetate (**1**)

While the formula scheme illustrates the preparation of (all-rac)-α-tocopheryl acetate the invention is not limited to that particular steric form and other steric forms can be obtained by using a phytyl starting material which has the appropriate stereoconformation. Thus, (RS,R,R)-α-tocopheryl acetate will be obtained when using (R,R)-phytol, (R,R,R)-isophytol, or (S,R,R)- isophytol or (RS,R,R)- isophytol or a (R,R)-phytyl halide.

Thus, in a first aspect, the present invention relates to a process for the preparation of 3-phytyl-2,3,6-trimethylhydroquinone-1-acetate (6) which comprises either

(a) C-alkylating 2,3,6-trimethylhydroquinone-1-acetate (4) with isophytol (2) or phytol in the presence of a sulfur (VI) catalyst of the formula $R\text{-}SO_2OH$, wherein R is hydroxy, halogen, aliphatic halocarbyl, or aliphatic or aromatic hydrocarbyl, in an aprotic organic solvent, or

(b) O-alkylating 2,3,6-trimethylhydroquinone-1-acetate (4) with a phytyl halide (3) in a polar aprotic organic solvent in the presence of a base and subjecting the so-obtained 4-O-phytyl-2,3,6-trimethylhydroquinone-1-acetate (5) to conditions resulting in a Claisen-Cope rearrangement.

In another aspect, the present invention relates to a process for the preparation of tocopheryl acetate (4) which comprises submitting 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (6) to conditions resulting in ring closure to produce the chromane ring system.

In still another aspect, the present invention relates to the novel compound, 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (6), especially the stereoisomers (*E,all-rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate, (*Z,all-rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate, (*E,R,R*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate, and (*Z,R,R*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate.

The C-alkylation of the compound (4) in accordance with the present invention can be carried out using a sulfur(VI) containing catalyst of the formula R-SO_2OH, wherein R is hydroxy, halogen, or aliphatic halocarbyl, or aliphatic- or aromatic hydrocarbyl. Examples of halocarbyl sulfonic acids are trifluoromethane sulfonic acid, examples of aliphatic hydrocarbyl sulfonic acids are methane sulfonic acid and ethane sulfonic acid, and examples of aromatic hydrocarbyl sulfonic acids are benzene and p-toluene sulfonic acid. Further sulfur(VI) containing catalysts which may be used are sulfuric acid and fluoro sulfuric acid. Preferred are catalysts which work in two-phase solvent systems, e.g. p-toluene sulphonic acid or trifluoromethane sulfonic acid. The catalyst may be present in an amount of from about 0.01 mol-% to about 1 mol-%, preferably in an amount of about 0.05 to about 0.1 mol-%, based on phytol or isophytol, respectively. Suitably, the reaction temperature for the alkylation is 293 K to 433 K, preferred are 353 K to 423 K, and most preferred 373 K to 400 K. Example of aprotic organic solvents for use in the C-alkylation reaction are polar solvents e.g. aliphatic and cyclic ketones, such as diethyl ketone and isobutyl methyl ketone, cyclopentanone and isophorone; aliphatic and cyclic esters and lactones, such as ethyl acetate, isopropyl acetate, and γ-butyrolactone, carbonates such as ethylene carbonate and propylene carbonate; and apolar solvents, e.g., aliphatic hydrocarbons, such as hexane, heptane and octane, and aromatic hydrocarbons, e.g. benzene, toluene and the xylenes. The reaction can be effected in a single solvent phase, e.g. in toluene alone as the solvent, or in a biphasic solvent system, e.g. in ethylene or propylene carbonate and heptane. A preferred solvent is an ethylene carbonate/heptane mixture (e.g., of about 1 : 1 by vol.). The isophytol or phytol may have the

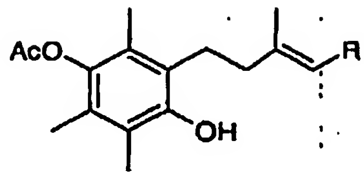
stereoconfiguration derived from natural phytol (R,R) or may be of any other stereoconfiguration, e.g., of the all-rac form.

For the O-alkylation of (4) the phytyl halide (3) is suitably a bromide or chloride. Preferred is phytyl bromide. As in the C-alkylation the phytyl moiety may have the stereoconfiguration of natural phytol (R,R) or may be of any other stereoconfiguration, e.g., of the all-rac form. The alkylation can be performed using conventional conditions for alkylation of phenolic systems, i.e. in the presence of a base such as sodium hydride,in a polar aprotic solvent as defined earlier. Preferred solvents are dimethyl formamide and dibutyl formamide.

The Claisen-Cope rearrangement reaction of compound (5) is suitably performed at temperatures below room temperature in the presence of an acidic catalyst, e.g. a Friedel-Crafts catalyst such as boron trifluoride etherate in a solvent such as a halogenated hydrocarbon, particularly carbon tetrachloride or mixtures of carbon tetrachloride and hexane, e.g. at about 245 K to 250 K.

The ring closure of 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (6) in accordance with the invention can be effected by treating (6) with an acidic catalyst in an aprotic organic solvent. Preferred solvents are polar aprotic solvents such as those specified above. The catalyst may be one as specified above for the C-alkylation of 2,3,6-trimethylhydroquinone-1-acetate (4). In a preferred embodiment of the invention, the same catalyst and the same solvent as used in the C-alkylation is used in the ring closure of 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (6).

It has been found that the compound (6) may isomerize to form the isomers, (*Z*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-hexadec-3-enyl)-phenyl ester (7), (*E*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-hexadec-3-enyl)-phenyl ester (8), and acetic acid 4-hydroxy-2,5,6-trimethyl-3-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester (9)



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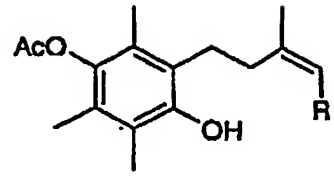

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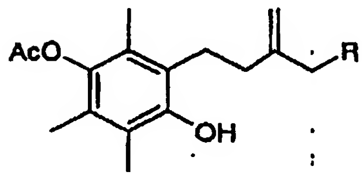

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R = $C_{15}H_{31}$

These isomers can be cyclized to form α-tocopheryl acetate in the same manner as described above for 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate (6). Accordingly, the invention also includes the cyclisation of (7), (8) and (9) either alone or together with (6). Compound (9) is a novel compound and, as such, is also an object of the present invention.

For the ring closure reaction the catalyst may be present in an amount of from about 0.01 mol-% to about 10 mol-%, preferably in an amount of about 0.1 to about 5 mol-%. The ring closure reaction is conveniently effected at temperatures from about 293 K to about 433 K, preferably from about 353 K to about 413 K.

2,3,6-Trimethylhydroquinone-1-acetate (4) may be obtained, e.g., by selective hydrolysis of 2,3,5-trimethylhydroquinone-diacetate as described in EP 1 239 045.

The following Examples illustrate the invention further.

Example 1

In a four-necked flask equipped with stirrer, water separator, and reflux condenser, 19.7 g (100 mmol) of trimethylhydroquinone-1-monoacetate and 25 ml of solvent (toluene, n-butyl acetate or diethylketone) were heated with stirring under argon atmosphere to reflux temperature (oil bath 413-418 K). After the addition of catalyst (see Table 1 below), 36.4 ml (100 mmol) of isophytol were added at a rate of 0.8 ml/min. The reaction mixture was heated under reflux for 30 min after completion of the addition of the isophytol. The reaction mixture was cooled and evaporated under reduced pressure. A viscous oil was obtained. For the yield of (all-*rac*)-α-tocopheryl acetate see Table 1.

Example 2

In a four-necked flask equipped with stirrer, water separator, and reflux condenser, 19.7 g (100 mmol) of trimethylhydroquinone-1-monoacetate and 25 ml of γ-butyrolactone were heated with stirring under argon atmosphere to approx. 383 K (oil bath 388 K). After the addition of catalyst (see Table 1), 36.4 ml (100 mmol) of isophytol were added at a rate of 0.8 ml/min. The reaction mixture was heated under reflux for 30 min after completion of the addition of the isophytol. The reaction mixture was cooled to 353 K and extracted three times with 50 ml of heptane. The combined heptane phases were evaporated under reduced pressure. A viscous oil was obtained. For the yield of (all-*rac*)-α-tocopheryl acetate see Table 1.

Example 3

In a four-necked flask equipped with stirrer, water separator, and a reflux condenser, 29.5 g (150 mmol) of trimethylhydroquinone-1-monoacetate, 120 g of ethylene carbonate and 150 ml of heptane were heated with stirring under argon atmosphere to reflux (oil bath 413 K). After the addition of catalyst (see Table 1), 36.4 ml (100 mmol) of isophytol were added at a rate of 0.8 ml/min. Approx. 1.8 ml water were collected after complete addition of the isophytol. The heptane was distilled off within approx. 20 min. Afterwards the reaction mixture was heated for 30 min at 398-403 K. The reaction mixture was cooled down to 353 K. 150 ml heptane were added to the carbonate phase. The reaction mixture was stirred for additional 10 min at 353-363 K. The mechanical stirrer was removed and the reaction mixture was cooled to 278 K. The heptane layer was separated and evaporated under reduced pressure. A viscous oil was obtained. For the yield of (all-*rac*)-α-tocopheryl acetate see Table 1.

Table 1: Reaction of isophytol (IP) and trimethylhydroquinone-1-acetate (TMHQ-1-MA) to (all-*rac*)-α-tocopheryl acetate (1) according to the Examples 1-3

Example	Catalyst	mol-%	Solvent	% (1)	% VE
1	p-TosOH	0.1	toluene	20.4	0.0
1	CF_3SO_3H	0.1	toluene	62.6	7.8
1	CF_3SO_3H	0.1	DEK	60.7	3.6
1	CF_3SO_3H	0.1	BuAc	54.8	6.7
2	p-TosOH	0.1	Bulac	14.2	0.3
2	H_2SO_4	0.1	Bulac	29.5	1.8
2	CH_3SO_3H	0.1	Bulac	10.2	0.1
2	CF_3SO_3H	0.1	Bulac	50.0	15.7
2	FSO_3H	0.1	Bulac	15.9	0.7
3	p-TosOH	0.1	EC/hept	78.1	0.6
3	p-TosOH	2.5	EC/hept	80.6	2.2
3	H_2SO_4	0.1	EC/hept	67.5	2.2
3	CH_3SO_3H	0.1	EC/hept	20.0	0.0
3	CH_3SO_3H	2.5	EC/hept	79.4	4.0
3	CF_3SO_3H	0.1	EC/hept	81.9	3.5
3	FSO_3H	0.1	EC/hept	67.0	3.0

The amount of catalyst is based on isophytol, the TMHQ-1-MA /IP ratio was 1:1 with the exception of PC and EC, here a 1.5:1 ratio was used, p-TsOH was used as monohydrate,

VE = vitamin E (unesterified), EC = ethylene carbonate, hept. = heptane, DEK = diethylketone, BuAc = n-butyl acetate, Bulac= γ-butyrolactone, yield based on isophytol.

Example 4

In a four-necked flask equipped with stirrer, water separator, and reflux condenser, 29.5 g (150 mmol) of 2,3,6-trimethylhydroquinone-1-monoacetate, 120 g of ethylene carbonate, and 150 ml of heptane were heated under argon atmosphere to reflux (oil bath 140°C). After the addition of catalyst (see Table 2 below), 36.4 ml (100 mmol) of isophytol were added at a rate of 0.8 ml/min. Approx. 1.8 ml water were separated after complete addition of the isophytol. Afterwards the reaction mixture was heated for 15 min under reflux. Stirring was discontinued and the reaction mixture cooled to 5°C. The heptane layer was separated and evaporated under reduced pressure. A viscous oil was obtained. For the yield of *(E,Z)*-(all-*rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-monoacetate (6) (*E:Z* = 2.2-2.4:1) see Table 2

Table 2: *C*-alkylation reaction of TMHQ-1-MA

Catalyst	mol-%	Solvent	% (6)	% (1)
p-TosOH	0.1	EC/hept	72.5	11.7
CF_3SO_3H	0.01	EC/hept	46.4	34.4
CH_3SO_3H	0.1	EC/hept	73.4	4.1
FSO_3H	0.05	EC/hept	62.3	17.4
H_2SO_4	0.1	EC/hept	51.8	29.3
H_2SO_4	0.05	EC/hept	74.5	1.4
CH_3SO_3H	2.5	EC/hept	79.4	34.4

The amount of catalyst is based on isophytol, p-TsOH was used as mono-hydrate, EC = ethylene carbonate, hept. = heptane, ratio EC/hept. = 120 g/150 ml, (1) = (all-*rac*)-α-tocopheryl acetate, yield based on isophytol, the ratio of TMHQ-1-MA to IP was 1.5 to 1.

Example 5

29.43 g (150 mmol) of 2,3,6-trimethylhydroquinone-1-monoacetate, 120 g of ethylene carbonate, 21.14 mg (0.1 mol %) of p-TsOH·H_2O, and 150 ml of heptane were heated to 373 K (oil bath 403 K) in a four-necked flask equipped with stirrer, water separator, and reflux condenser. Isophytol (36.18 ml, 100 mmol) was added at a rate of 0.8 ml/min under reflux. After heating for an additional 5 min the reaction mixture was cooled to room temperature. The heptane layer was separated and the solvent evaporated under reduced pressure (313 K, 10 mbar). 49.43 g of a yellowish oil was obtained which contained according to gas chromatography, 68 % of *(E,Z)*-(all-*rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-monoacetate (6), *E/Z*-ratio 2.2:1, (yield 71 %), and 2 % of (all-*rac*)-α-tocopheryl-acetate.

The above obtained oil was purified further by column chromatography on silica gel (Merck 109385.1000, Kieselgel 60 (0.040-0.063 mm)) [eluent *n*-hexane 100% (1L) --> *n*-hexane/ Et_2O 10:1 (1.1L) --> *n*-hexane/Et_2O 10:2 (1.7L)], to afford (6) as a light yellow oil with purity of 89.4%, E/Z-ratio about 3:1. The oil still contained 0.70% (all-*rac*)-α-tocopheryl acetate.

E- and Z-isomers could be separated by HPLC using a Spherisorb Si 5 μm column and isopropyl acetate/n-hexane 4:100 as the mobile phase.

E- Isomer:

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.78-0.93 (m, 12 H, 4 CH_3), 0.97-1.57 (m, 19 H, aliph.), 1.80 (s, 3 H, $=CC\underline{H}_3CH_2$), 1.98 (t, J = 7.4 Hz, 2 H, $=CCH_3C\underline{H}_2$), 2.04, 2.07, 2.14 (each s, 3 H, Ar-CH_3), 2.33 (s, 3 H, CH_3CO), 3.36 (d, J = 6.8 Hz, 2 H, $ArC\underline{H}_2$), 5.08 (s, 1 H, OH), 5.13 (t, J = 6.6 Hz, 1 H, CH=) ;

IR (film): 3500s, 2927s, 2868s, 1762s, 1745s, 1577w, 1462s, 1369s, 1225s, 1075m, 1010w, 514s ;

Z- Isomer:

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.79-0.96 (m, 12 H, 4 CH_3), 1.00-1.57 (m, 19 H, aliph. H), 1.72 (s, 3 H, $=CC\underline{H}_3CH_2$), 2.03, 2.06, 2.14 (each s, 3 H, Ar-CH_3), 2.20 (t, J = 7.8 Hz, 2 H, $=CCH_3C\underline{H}_2$), 2.33 (s, 3 H, CH_3CO), 3.36 (d, J = 6.4 Hz, 2 H, $ArC\underline{H}_2$), 5.06 (s, 1 H, OH), 5.13 (t, J = 6.6 Hz, 1 H, C$\underline{H}$=);

IR (film): 3496s, 2926s, 2868s, 1761s, 1745s, 1577w, 1462s, 1369s, 1227s, 1076m, 1056m, 1010w, 516s.

Example 6

From the *(E,Z)*-(all-*rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-monoacetate as obtained in Example 5, the isomer, (all-*rac*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester (9) was obtained as follows:

In a first step traces of ethylene carbonate, phytadienes, and TMHQ-1-MA (5) were distilled off at 363 K and 2.5×10^{-2} mbar. The distilled material was submitted to HPLC mobile phase: isopropyl acetate/n-hexane 4:100, column: Spherisorb Si, 5 µm). Besides the isomers, (*Z,RS,RS*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-hexadec-3-enyl)-phenyl ester (7) and (*E,RS,RS*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-hexadec-3-enyl)-phenyl ester (8), the isomer (all-*rac*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester (9) was identified (HP gaschromatograph (6890) with split-injector and HP autosampler (7673), HP mass selective detector (5973), Column: 5 % phenyl-methyl siloxane fused silica (Restek), 30 m x 0.28 mm, film 0.5 µm, carrier gas: He, flow 1.5 ml/min (constant flow), split ration approx. 1:25):

(all-*rac*)-acetic acid 4-hydroxy-2,3,6-trimethyl-5-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester (9):

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 0.77-0.92 (m, 12 H, 4 CH_3), 0.98-1.55 (m, 17 H, aliph. H), 2.14, 2.18, 2.72 (each s, 3 H, Ar-CH_3), 2.02-2.09 (m, 2 H, =C$\underline{H_2}$), 2.14-2.18 (m, 2 H, =C$\underline{H_2}$) 2.33 (s, 3 H, CH_3CO), 2.72-2.77 (m, 2 H, ArC$\underline{H_2}$), 4.58 (s, 1 H, OH), 4.80, 4.83 (each s, 1 H, C$\underline{H_2}$=);

GC-MS (EI): m/z = 430 [M^+-C_2H_2O, 75 %], 207 [M^+-$C_{15}H_{32}$, 29 %], 165 [430-$C_{15}H_{32}$, 100 %].

Example 7

A 0.34 to 0.52 M stock solution of (*E*/*Z*)-(all-*rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-monoacetate (6) in the used solvent (toluene, heptane, diethylketone, *n*-butyl acetate or γ-butyrolactone) was prepared.

2.5 ml (for heptane 1.5 ml and 1.2 g EC) of this solution was transferred to a Schlenk tube under argon, the catalyst (see below and Table 3) was added, and the reaction mixture was

heated for 1 h at 100°C (oil bath temperature). Then the solution was cooled to room temperature and the solvent removed under reduced pressure (in the case of toluene, diethylketone, and *n*-butyl acetate). In the case of γ-butyrolactone the reaction mixture was extracted three times with approx. 1.5 ml heptane. For the biphasic system, the layers were separated and the heptane phase was concentrated in vacuo.

Table 3 : Ring-closure reaction of *(E,Z)*-(all-*rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-monoacetate (6)

Catalyst	mol-%	Solvent	% (6)	% (1)	% VE
CH_3SO_3H	0.1	EC/hept	87.9	0.9	0
CH_3SO_3H	1.16	toluene	44.5	53.8	0
CH_3SO_3H	0.116	DEK	97.5	0.5	0
CH_3SO_3H	0.1	BuAc	99.6	0.6	0
CH_3SO_3H	0.1	Bulac	94.0	2.2	0
CF_3SO_3H	0.1	EC/hept	18.6	84.9	0
CF_3SO_3H	1.16	toluene	0	96.1	3.3
CF_3SO_3H	0.116	DEK	2.7	97.3	0.2
CF_3SO_3H	0.1	BuAc	17.0	84.7	0.1
CF_3SO_3H	0.1	Bulac	0	100.9	1.7

The amount of catalyst is based on starting material (6), p-TsOH was used as monohydrate, VE = vitamin E (unesterified), EC = ethylene carbonate, hept = heptane, DEK = diethylketone, BuAc = n-butyl acetate, Bulac = γ-butyrolactone, (1) = (all-*rac*)-α-tocopheryl acetate.

Example 8

In analogy to the procedure of Example 7 but extending the reaction time and increasing the amount of catalyst the results as shown in Table 4 were obtained:

Table 4 : Ring-closure reaction of *(E,Z)*-(all-*rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-monoacetate (6)

Catalyst	reaction time [min]	Temp.(bath) °C	mol-%	Solvent	% (1)	% VE
CH_3SO_3H	180	120	5.0	toluene	100	0.8
CH_3SO_3H	180	120	5.0	DEK	72.9	0.1
CH_3SO_3H	180	120	5.0	BuAc	69.4	0.2
CH_3SO_3H	180	120	5.0	Bulac	97.9	0.8
p-TosOH	120	100	2.56	EC/hept	96.3	0.1
H_2SO_4	180	100	6.25	EC/hept	97.8	1.5
H_2SO_4	120	120	2.5	EC/hept	100.3	0.6

The amount of catalyst is based on starting material (6), p-TsOH was used as monohydrate, VE = vitamin E (unesterified), EC = ethylene carbonate, hept = heptane, DEK = diethylketone, BuAc = n-butyl acetate, Bulac = γ-butyrolactone, (1) = (all-*rac*)-α-tocopheryl acetate.

Example 9

1.4 mg ($3.15 \cdot 10^{-3}$ mmol) (all-*rac*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester (9) were dissolved in 0.1 ml PC and 0.2 ml heptane. After addition of 0.5 mg ($2.63 \cdot 10^{-3}$ mmol) p-TsOH·H_2O the reaction mixture was heated for 90 min to 393 K (oil bath). A GC of the heptane phase showed the cyclisation product (all-*rac*)-α-tocopheryl acetate in 98.5 % purity (GC-area %).

Example 10

To 2.1 g (43.7 mmol) of sodium hydride dispersion (50 % in mineral oil) which was freed from mineral oil by washing with hexanes there was added under Ar atmosphere 90 ml of dimethylformamide and, after cooling to ca. 278 K, 7.38 g (38 mmol) of

2,3,6-trimethylhydroquinone-1-monoacetate. After ca 30 min, 16.4 g (45.6 mmol) phytyl bromide (freshly prepared from natural phytol) in 30 ml of dimethylformamide were added dropwise at 273 K over a period of 15 min. The recation mixture was stirred for 1 hr while warming to ambient temperature. The mixture was then quenched with 300 ml of deionized water and 200m ml of ether. The organic layer was separated and the aqueous layer extracted with ether. The combined organic layers were washed successively with cold 2N NaOH, water and brine; dried over sodium sulfate, filtered and evaporated to afford 20.0 g of an amber liquid. Flash chromatography of this material on silicagel using hexanes/ethyl acetate 1% →3 % yielded 15.6 g of

(*E,R,R*)-4-O-phytyl-2,3,6-trimethylhydroquinone-1-acetate, as a light yellow oil,

$[\alpha]_D^{25} = -0.44°$ (1.13 % in hexanes).

Example 11

In analogy to Example 10, a different batch of natural phytol containing small amounts of (Z,R,R)-phytol was used. After conversion of the phytol to phytyl bromide, and subsequent O-alkylation reaction with 2,3,6-trimethylhydroquinone-1-monoacetate, (E/Z, R,R)-4-O-phytyl-2,3,6- trimethylhydroquinone-1-acetate (5) was obtained after chromatographic purification as a yellow oil having an E/Z ratio of 98.7:1.3 (HPLC analysis).

Example 12

6.76 g (14.3 mmol) of (*E,R,R*)-4-O-phytyl-2,3,6-trimethylhydroquinone-1-acetate and 100 ml of carbon tetrachloride was cooled to ca. 243 K and 0.44 ml (3.58 mmol) of boron trifluoride etherate was added dropwise. The solution was stirred at 245 K to 251 K while monitoring the course of the reaction by TLC. After 18 min when the TLC showed complete conversion of the starting material the reaction was quenched by the addition of 10 ml of saturated $NaHCO_3$ solution. The mixture was poured into 200 ml of deionized water and 200 ml of ether. The layers were separated, the auqueous phase extracted with ether und the combined organic phases washed successively with deionized water and brine and dried over sodium sulfate. The solution was filtered and evaporated to yield 7.1 g

of a yellow oil which was chromatographed on silicagel 60 (70-230 mesh) with hexanes, hexanes containing 2 % ethyl acetate and hexanes containing 5 % ethyl acetate. There was obtained 1.36 g of (RS,R,R)-α-tocopherol acetate and 4.00 g of (*E*,*R*,*R*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate, $[\alpha]_D^{25} = 0.10°$ (1.98 % in hexane).

<u>What is claimed is:</u>

1. A process for the preparation of 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate which comprises C-alkylating 2,3,6-trimethylhydroquinone-1-acetate with isophytol or phytol in the presence of a sulfur (VI) catalyst of the formula R-SO_2OH, wherein R is hydroxy, halogen, aliphatic halocarbyl, or aliphatic or aromatic hydrocarbyl, in an aprotic organic solvent.

2. A process as in claim 1 wherein the sulfur (VI) catalyst is sulfuric acid or fluoro sulfuric acid.

3. A process as in claim 1 wherein the sulfur (VI) catalyst is an aliphatic halocarbyl sulfonic acid or an aliphatic or aromatic hydrocarbyl sulfonic acid.

4. A process as in claim 1 wherein the sulfur (VI) catalyst is methane sulfonic acid, trifluoromethane sulfonic acid or p-toluene sulfonic acid.

5. A process as in any one of claims 1-4 wherein the catalyst is used in an amount of from about 0.01 mol-% to about 1 mol-% based on isophytol or phytol.

6. A process as in any one of claims 1-5 wherein the solvent is a two-phase solvent system.

7. A process as in claim 6 wherein one phase of the two-phase solvent system is ethylene carbonate or propylene carbonate and the other phase is heptane, hexane or octane.

8. A process as in claim 6 wherein the solvent system is ethylene carbonate/heptane.

9. A process for the preparation of 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate which comprises O-alkylating 2,3,6-trimethylhydroquinone-1-acetate with a phytyl halide in a polar aprotic organic solvent in the presence of a base and subjecting the so-obtained 4-O-phytyl-2,3,6-trimethylhydroquinone-1-acetate to conditions resulting in a Claisen-Cope rearrangement.

10. A process as in claim 9 wherein the O-alkylation is effected in dimethyl formamide in the presence of sodium hydride.

11. A process as in claim 9 wherein the Claisen-Cope rearrangement is effected by treating the 4-O-phytyl-2,3,6-trimethylhydroquinone-1-acetate with boron trifluoride etherate.

12. A process for the preparation of tocopheryl acetate which comprises treating 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate with an acidic catalyst in an aprotic organic solvent.

13. A process as in claim 12 wherein the catalyst is a sulfur (VI) catalyst of the formula R-SO_2OH, wherein R is hydroxy, halogen, aliphatic halocarbyl, or aliphatic or aromatic hydrocarbyl.

14. A process as in claim 13 wherein the sulfur (VI) catalyst is sulfuric acid or fluoro sulfuric acid.

15. A process as in claim 13 wherein the sulfur (VI) catalyst is an aliphatic halocarbyl sulfonic acid or an aliphatic or aromatic hydrocarbyl sulfonic acid.

16. A process as in claim 13 wherein the sulfur (VI) catalyst is methane sulfonic acid, trifluoromethane sulfonic acid or p-toluene sulfonic acid.

17. A process as in any one of claims 12-16 wherein the catalyst is used in an amount of from about 0.1 mol-% to about 5 mol-% based on 3-phytyl-2,3,6-trimethylhydroquinone-1-acetate.

18. A process as in any one of claims 12-17 wherein the solvent is a two-phase solvent system.

19. A process as in claim 18 wherein one phase of the two-phase solvent system is ethylene carbonate or propylene carbonate and the other phase is heptane, hexane or octane.

20. A process as in claim 18 wherein the solvent system is ethylene carbonate/heptane.

21. A process for the preparation of tocopheryl acetate which comprises C-alkylating 2,3,6-trimethylhydroquinone-1-acetate with isophytol or phytol in the presence of a sulfur (VI) catalyst of the formula R-SO_2OH, wherein R is hydroxy, halogen, or aliphatic or aromatic hydrocarbyl, in an aprotic organic solvent and treating the so-obtained 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate or an isomer thereof selected from (*Z,RS,RS*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-hexadec-3-enyl)-phenyl ester (7), (*E,RS,RS*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-hexadec-3-

enyl)-phenyl ester (8), and (all-*rac*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester (9)

with an acidic catalyst in an aprotic organic solvent.

22. A process for the preparation of tocopheryl acetate which comprises O-alkylating 2,3,6-trimethylhydroquinone-1-acetate with a phytyl halogenide in a polar aprotic organic solvent in the presence of a base, subjecting the so-obtained 4-O-phytyl-2,5,6-trimethylhydroquinone-1-acetate to conditions resulting in a Claisen-Cope rearrangement and treating the so-obtained 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate or an isomer thereof selected from (*Z*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-hexadec-3-enyl)-phenyl ester (7), (*E*)-acetic acid 4-hydroxy-2,5,6-trimethyl-3-(3,7,11,15-tetramethyl-hexadec-3-enyl)-phenyl ester (8), and acetic acid 4-hydroxy-2,5,6-trimethyl-3-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester (9) with an acidic catalyst in an aprotic organic solvent.

23. 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate.

24. (*E,all-rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate.

25. (*Z,all-rac*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate.

26. (*E,R,R*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate.

27. (*Z,R,R*)-3-phytyl-2,5,6-trimethylhydroquinone-1-acetate.

28. acetic acid 4-hydroxy-2,3,6-trimethyl-5-[3-(4, 8,12-trimethyl-tridecyl)-but-3-enyl]phenyl ester.

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